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FINAL PROGRESS REPORT

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"Microstimulation of the Lumbosacral Spinal Cord"

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INTRODUCTION

The overall goals of this contract are to develop a method of chronic microstimulation of the sacral spinal cord of the cat to effect micturition, and to evaluate the effects of the electrical stimulation on surrounding tissues. At HMRI we have developed microstimulation to the point where microelectrodes can be implanted chronically into the feline cerebral cortex and into the cochlear nucleus with a minimum of tissue injury, and we have made considerable progress in the development of protocols for safe and effective stimulation with arrays of closely-spaced microelectrodes.

In the spinal cord, we have quite reproducibly effected micturition by microstimulation of the preganglionic, parasympathetic nuclei of the S_2 segment of the cat spinal cord in both acute and chronic experiments using one or more activated iridium microelectrodes. However, in chronic implants in the spinal cord we have encountered some problems of electrode instability and resulting tissue injury, that appear to be related to the special environment of this site. One source of difficulty appears to be related to the rostro-caudal movement of the cord relative to the dura as the animal extends it hindlimbs or arches its back, and this may be linked to the manner in which the electrode cables are secured. Deformation of the tissue (dimpling) during manual insertion of single or multiple electrode arrays as well as trauma due to suturing of the dura after electrode implantation may also contribute to the tissue injury. We have observed that the evoked responses recorded from the ventral roots and the changes in intravesicular and intraurethral (EUS) pressures induced by microstimulation often shift markedly after the dura is sutured over newly-implanted microelectrodes. However, the dura must be closed in some fashion to prevent leakage of CSF, and to keep the array from drifting up out of the cord. Also, the method of closure must not permit the spinal roots or the subdural segment of the cable to become entrapped within connective tissue. These problems, and others, have been addressed in this contract period.

Physiologic and histologic results of microstimulation.

One of the mandates of this contract period was to evaluate the physiologic and histologic effects of moderately prolonged stimulation (12 hours per day on 2 successive days) on the neurons and glia adjacent to the electrodes.

We have reported such studies in eighteen animals which were implanted chronically with individual microelectrodes (QPR's 1-9). Successful stimulations were carried out in 15 animals in which one or more electrodes were functioning and in which evoked potentials could be recorded after an implant period of 30-45 days. The electrical stimulation parameters were 20 Hz, 80 μA, 150 μsec/ph (charge/ph of 12 nC/ph and charge density of 1600 $\mu C/cm^2$).

In most experiments, depression of stimulation-induced neuronal excitability (SIDNE) was either absent, or the stimulation resulted in only moderate depression. The low-incidence of SIDNE probably is due to the low stimulus frequency (20 Hz), which is appropriate for the intended clinical applications. However, in QPR 8, we reported one animal when the stimulation resulted in an apparent cumulative effect, i.e., the occurrence of mild SIDNE during the first 12-hour period of stimulation with a greater depression by the end of the second 12-hour period. It should be noted that these stimulations were continuous, and are far more prolonged than would be required for effecting electromicturition.

However, the level of mechanically-induced neural damage often made it difficult to determine the extent, if any, of electrically-induced damage. The former included fibrosis associated with the electrode tracks, trauma to the pia and leptomeningeal vessels, inflammatory foci, myelin changes including Wallerian degeneration, lipid-laden macrophages and, on several occasions, CSF infiltration (extracellular edema) due to disruption of the central canal. In general, histologic observation of neurons correlates well with the physiologic observations, in that neuronal injury attributable to the electrical stimulation has been minimal.

Evaluation of various configurations of arrays for microstimulation of the spinal cord.

We began this contract period using individual microelectrodes supported by a substrate fashioned from a silicone tube (508 μm ID, 940 μm OD, 6 mm long) that was halved lengthwise, and perforated either with holes (203 μm in diameter) or transverse slits. This "hemicylinder" was placed subdurally over the dorsum of the cord. Four activated iridium microelectrodes (50 μm long, 2.8 mm long, with 2000 μm^2 exposed stimulating surfaces) were implanted manually at approximately the dorsal midline and angled laterally to the target at about 10 degrees. The electrodes were advanced individually into the cord through the matrix, until good elevation of bladder pressure was produced by microstimulation (QPR 1-2). Due to persistent mechanically-induced trauma by this array (compression and distortion of the dorsal cord, connective tissue scars associated with electrodes which moved appreciably from the original insertion site), we abandoned the use of an array matrix. Four activated iridium electrodes (50 μm dia, 2.8 μm long) were simply inserted manually at approximately the dorsal midline and angled laterally at approximately 10° (QPR's 3-5). A reduction in the diameter of the electrodes from 50 to 25 μm and reduction of the dural incision to small slits failed to prevent mechanically-induced trauma in chronic spinal implants. Histologic findings included scarring adjacent to many electrodes and occasional disruption of the central canal, resulting in edema from subsequent CSF leakages. Vascular hyperplasia was a consistent finding and frequent inflammatory responses were present.

The smaller electrode diameter appeared to reduce the trauma of insertion of the electrodes, but widespread scarring occurred in most animals. We concluded that individual electrodes implanted through slits or holes in the matrix or implanted individually without matrixes were basically positionally unstable. It was not clear whether the instability was due to the design of the electrodes themselves or to traction on the electrode imposed by the cables, or to both.

To address these problems we initiated several changes in our implantation procedure. First, a model of the feline spinal cord was cast from a Turgid agar molded

to the approximate size and shape of the feline lumbosacral cord. The transparency of the model allowed visualization of electrodes of various diameters (QPR 9). Electrodes 24 or 34 μm in diameter were inserted into the model while observing their penetration, with the aid of a surgical microscope. The 24 μm diameter electrodes tended to bend and to follow divergent paths, whereas the 34 μm diameter electrodes did not bend during manual insertion. We concluded that 34 μm is probably the minimum electrode diameter that can be inserted into the spinal cord without excessive bending.

To address the problems outlined above we have ceased all microstimulation experiments and are currently evaluating the contribution of the array cable, the method of stabilizing the cable and the method of closing the dura, to the mechanical stability of the intraspinal microelectrode arrays and also to the mechanically-induced tissue injury.

Our present spinal array, which is now under evaluation, consists of a solid epoxy matrix (2 mm in length and approximately 0.75 mm in width) upon which is mounted 3 activated iridium microelectrodes of lengths, 1.1, 1.2 and 1.4 mm, spaced 500 μm apart. Initially, the microelectrodes had blunt tips (radius of curvature 5-6 μm).

We have also employed two types of axial introducers mounted to the spinal apparatus, and we hyperventilate the animal for 5 minutes prior to turning off the respirator and inserting the array, in order to reduce movement of the cord, due to respiratory movements. Initial results with implantation of these electrodes without cables showed considerable improvement over previous results, in which there was extensive tissue injury and glial scarring around the electrode tracks. However, these blunt electrodes induced marked displacement and rotation of the cord as they were being inserted and this also altered the trajectory of the microelectrodes from their initial targets.

In the next Quarter (QPR 11) we used sharper microelectrodes (radius of curvature of 1.5 to 2 μm) to reduce dimpling and rotation of the cord during insertion with an axial introducer. These arrays were implanted without cables. The spinal dura was not sutured closed but an 8.0 monofilament suture was run between the left and

right leaves of the dura, over the tops of the implanted arrays, and then tied loosely to hold the arrays in place. A patch of fascia was then placed over the cord prior to closing the musculature over the laminectomy. Results of this study indicated that these sharper electrodes could be inserted into the lumbosacral cord with little trauma to the parenchyma of the cord, while avoiding the microhematomas that we have observed in the cerebral cortex and cochlear nucleus when sharp microelectrodes are used.

A disturbing histologic feature in this series (QPR 11) was frequent meningeal inflammation and sporadic presence of inflammatory foci along the electrode shafts. We suspect the cause of the inflammation to be incomplete curing of the Epoxylite insulation, resulting in a release of epoxy monomers. Accordingly, we have modified the curing schedule for the Epoxylite insulation to ensure complete polymerization.

During the past quarter, our evaluation of dummy electrodes with and without cables has continued. The cables were fabricated from pure platinum (50 μm in diameter) insulated with Teflon. These cables are very flexible and malleable. They were sutured to the spinal dura about 10 mm rostral to the arrays. One of two methods was used to insert the electrodes into the sacral cord. In all animals prior to SP-97, the array was held by a vacuum onto the end of an axial introducer mounted on the parallel bar of the spinal apparatus. The dorsal roots were retracted with a pair of forceps, and the electrodes were inserted into the cord at a low velocity (approximately 1 mm/sec). This method presented two problems. There was often considerable dimpling and rotation of the cord during insertion of the microelectrodes, and this may have contributed to the small amount of mechanically-induced neural injury seen in this series. Also, it was difficult to retract the dorsal roots sufficiently so as to insert the microelectrodes into the lateral cell column (the preganglionic parasympathetic nucleus). Preliminary histologic results showed some neuronal chromatolysis in the first animal which was attributed to multiple insertions of the array (to avoid spinal roots and optimize the angle of insertion). However, in this animal as well as the second (single insertion), there was a distinct reduction of gliotic scarring and the tracks were

well defined, leaving adjacent parenchymal tissue relatively undisturbed and normal-appearing. Also, the cables did not dislodge the arrays, prior to their encapsulation with connective tissue. These are encouraging findings relative to the prospect of being able to clearly distinguish between mechanically and electrically induced neural damage when we resume chronic microstimulation experiments.

In the two most recent implants of the past quarter, the microelectrodes were inserted with the aid of a modified tool designed to insert microelectrodes into the human cochlear nucleus. Prior to its deployment, the microelectrode array is enclosed and protected within the end of the instrument's barrel. A vacuum of approximately 400 mm Hg holds the array firmly against the end of a hollow sliding piece within the barrel. The barrel also is used to retract the dorsal roots, allowing the array to be inserted more laterally. Since the insertion velocity is higher (approximately 1 m/sec), there is much less dimpling and rotation of the cord as the electrodes are being inserted.